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(19)

(54) IMPROVEMENTS IN OR RELATING TO BROPARESTROL BASED THERAPEUTIC COMPOSITIONS

(71) We, LAROCHE NAVARRON S.A., (formerly known as Laboratoires Laroche Navarron), a French Body Corporate of 20, rue Jean Jaurès, 92800 Puteaux, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

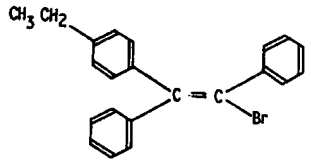
This invention relates to a new therapeutic composition containing, as active ingredient, the *trans* Broparestrol isomer.

Broparestrol or 1-bromo-2-(4-ethyl-phenyl)-1,2-diphenylethylene, obtained by chemical synthesis (N.P. Buu Hoï, Bull. Soc. Chim. Fr., 1946, 17) is a mixture of both the *cis* and *trans* isomers.

Each of said isomers was isolated in a state of high purity by fractional crystallization.

The structures of both the *cis* and *trans* components of Broparestrol were ascertained by analysis of the nuclear magnetic resonance (NMR) spectra and confirmed by radiocrystallography (J. M. Fornies-Marquina, C. Courseille, B. Busetta and M. Hospital, Crystal Structure Communication, 1972, *1*, 261—264).

Said physical-chemical investigations demonstrated that the *trans* isomer of Broparestrol may be represented as follows:



trans-isomer

Broparestrol, i.e., the mixture of the *cis*- and *trans*-isomers, which contains about 40% *cis*-isomer and about 60% *trans*-isomer, is already used for therapeutic purposes due to its low oestrogenic properties. Under the tradename Longestrol, it is used at an average daily dose of three 25 mg tablets, typically for the treatment of mammary disorders and to control metastases of the neoplasms of the endocrinogenital system.

Applicant has discovered that the two Broparestrol isomers possess in fact different specific properties and that the *trans* Broparestrol isomer constitutes a new therapeutically useful active ingredient which, due to its properties, is found to differ from the *cis* Broparestrol isomer and from the heretofore therapeutically used mixture of both the *cis* and *trans* isomers.

Particularly, Applicant has found that, while all said materials exhibit an action of competitive dualism type in their action with respect to oestrogens, i.e., a potentiation of the effects of low oestrogen dosages and an antagonism with respect to high oestrogen dosages, the modulating effect of the *trans* Broparestrol isomer is found to differ from that of the *cis* isomer and also from that of the mixture of the *cis* and *trans* isomers, because the antagonistic effect is highly predominant in the

case of the *trans* isomer whereas the synergistic effect is predominant in the case of the *cis* isomer.

Thus, this invention relates to a therapeutic composition having, in particular, a modulating or regulating effect on the effects of oestrogens, which contains the *trans* Broparestrol isomer as active ingredient and is substantially free of the *cis*-isomer, together with a pharmaceutically acceptable carrier.

The therapeutic composition of this invention may be formulated in a form suitable for oral or sub-cutaneous administration.

Pharmaceutical formulations suitable for oral administration include capsules, tablets, and suspensions. The capsules and tablets may typically contain 10—300 mg of the *trans* Broparestrol isomer, and preferably 10—50 mg.

Pharmaceutical formulations suitable for sub-cutaneous administration include injectable solutions in an acceptable solvent such as olive oil. Each ampoule may typically contain 3—200 mg of the *trans* Broparestrol isomer, and preferably 3—50 mg.

The *trans* Broparestrol isomer may be administered to human patients at a daily dosage of 0.3—10 mg/kg by the oral route and at a daily dosage of 0.05—3 mg/kg by the sub-cutaneous route.

The *trans* Broparestrol isomer is predominantly applicable in the treatment of female patients in the following cases:

—in the treatment of disorders related to a hormonal excess and typically:
—in the treatment of hormone-dependent mammary cancers,
—in the treatment of menopausal and post-menopausal disorders,
—to correct the effects of oral contraceptives consisting of oestrogen-progestational agent combinations,
—also as contraceptive agent due to its antifertilizing action, and

in male patients:

—in the treatment of hormone-dependent cancers of the prostate.

When applied to counteract the secondary effects of oral contraceptives, the *trans* Broparestrol isomer may be administered to female patients either independently from the oral contraceptive, or in combination with the latter.

Therefore, this invention includes also within its scope combinations of the *trans* Broparestrol isomer with oral contraceptives, which combinations exhibit the primary effects of oral contraceptives without their objectionable side-effects. Useful oral contraceptives include combinations of an oestrogen such as Ethinyl oestradiol or Mestranol and of a progestational drug such as Norgestrel, Norethisterone acetate, Quingestanol acetate and Lynoestrenol.

Results of pharmacological investigations which demonstrate the valuable properties of the *trans* Broparestrol isomer, particularly as compared to the *cis* Broparestrol isomer and to the mixture of the *cis* and *trans* Broparestrol isomers are given below.

I — Comparative uterotrophic action

a) Material and Method

α-Procedure

Use was made of the Lauson test in 2550 Sprague Dawley impuberal female rats (21 days, 40g±2 g). The animals were distributed into 85 groups of 30 animals each and were administered the test material or its carrier (1 reference group for each test) for three consecutive days.

The animals were sacrificed on the fourth day. After ether anesthesia and bleeding, the uteri were dissected and weighed in a fresh condition.

The test materials were dissolved in virgin olive oil and administered orally at a uniform volume of 0.2 ml/20 g.

The materials used were Ethinyl oestradiol, *trans* Broparestrol, *cis* Broparestrol and a 60 *trans*/40 *cis* Broparestrol mixture.

β—Expression of the results

The uterotrophic action is evaluated by the percent weight variation of the uterus of the treated animals with respect to that of the reference animals.

The effects are represented by an action (with respect to the maximum effect of the Ethinyl oestradiol reference) vs/dosage (as moles/kg) diagram.

The affinities and intrinsic activities were then calculated.

In this respect, it should be remembered that when a drug or agonist A becomes attached to a receptor R, thus forming a complex RA

$$A+R \rightleftharpoons Ra$$

and when: E_A=the effect of agonist A at a dosage of [A]
E_M=the maximum biological effect obtainable
E_{AM}=the maximal effect obtainable with agonist A

$$\frac{E_A}{E_M}=\frac{\alpha}{\frac{1+K_A}{[A]}}$$

Affinity is defined as being the value

$$\frac{1}{K_A}$$

and intrinsic activity is defined by the

$$\frac{E_{AM}}{E_M}=\alpha \text{ ratio}$$

At one-half the effect

$$\frac{E_A}{E_{AM}}=\frac{1}{2}, K_A=[A],$$

pD_{50} is the co-logarithm of the agonist concentration which produces 50% of the maximum effect.

b) Results

1) Action of the individual products *per se*

The results obtained are given in Table I (as percent weight variation of the uterus/vs the maximum effect of Ethinyl oestradiol E_A/E_M) and illustrated in Fig. 1.

TABLE I

Uterotrophic action of the compounds *per se*

Dosage (g/kg)	10^{-7}	10^{-6}	2.5×10^{-6}	5×10^{-6}	10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}	5×10^{-1}
Ethinyl oestradiol	0.55	27.6	64	85.5	96.3	100	–	–	–	–
Cis-Broparestrol	–	–	–	–	7.9	9.9	32	60	83.3	85.6
Broparestrol	–	–	–	–	3.4	17.4	36.7	59.5	69	66
Trans-Broparestrol	–	–	–	–	6.6	20.5	28.6	35.2	39.4	35

Both the *cis* and *trans* isomers and their admixture have an uterotrophic action and, thus, behave like oestrogenomimetic drugs (Fig. 1). However, their agonistic actions—characterized by the intrinsic activity—are markedly differentiated and follow the reverse law of their affinities, as apparent from following Table II which gives both the affinity and the intrinsic activity for each material.

TABLE II

Product	Uptake	Agonistic action
	Affinity (pD_2)	Intrinsic activity a
Ethinyl oestradiol	8.20	1.00
trans-Broparestrol	6.80	0.375
Broparestrol	5.55	0.690
cis-Broparestrol	4.95	0.790

Ethinyl oestradiol is a total agonist which exhibits the strongest affinity and maximum intrinsic activity.

cis-Broparestrol is a partial agonist which exhibits a very strong intrinsic activity, but the lowest affinity. Thus, it is very weakly taken up, but it is capable of exhibiting a good oestrogenic action at high dosages.

Broparestrol (mixture of *cis*- and *trans*-isomers) is the partial agonist which exhibits both average affinity and average intrinsic activity.

Of all the partial agonists, *trans*-Broparestrol is the one which exhibits the lowest oestrogenomimetic activity together with one of the highest uptake, after Ethinyl oestradiol.

2) Interaction of the different products with Ethinyl oestradiol

In another series of tests, Ethinyl oestradiol was administered simultaneously with the *trans* Broparestrol isomer, the *cis* Broparestrol isomer and the mixture of both isomers (60/40), respectively.

The results obtained with the *trans* Broparestrol isomer, the mixture of both isomers (60/40) and the *cis* Broparestrol isomer are illustrated in Figs. 2, 3 and 4, respectively. On the diagrams of said Figs. 2—4, the relative uterotrophic effect E_A/E_M (Effect observed/maximum effect observed with Ethinyl oestradiol) is plotted as a function of the log of the Ethinyl oestradiol dosage (mole/kg).

A modulation of the uterotrophic action of Ethinyl oestradiol (—o—) by the *trans* Broparestrol isomer, the mixture of both isomers, and the *cis* Broparestrol isomer, administered simultaneously at dosages of 10^{-3} g/kg (—●—) and 10^{-2} g/kg (—Δ—) is apparent from Figs. 2, 3 and 4, respectively.

It is apparent that the three products enter into a competitive dualism at different levels with Ethinyl oestradiol. They are synergistic at low Ethinyl oestradiol dosages and potentiate the minimum effects; they are antagonistic at high Ethinyl oestradiol dosages, inducing a maximum response which is lower than that of Ethinyl oestradiol. In addition, the values noted are reported in following Table III.

TABLE III

Uterotrophic effect (percent weight variation of the uterus with respect to the controls and compared to the maximum value of Ethinyl oestradiol)

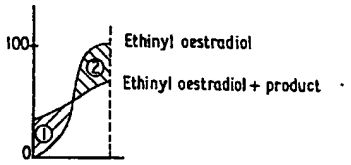
	Dosage g/kg	ETHINYL OESTRADIOL						
		0	10^{-7}	10^{-6}	2.5×10^{-6}	5×10^{-6}	10^{-5}	10^{-4}
$\bar{m}$ reference groups	0	0	5.5	27.6	64	85.5	96.3	100
trans-Broparestrol	10^{-3}	28.6	21.2	21.3	27.8	28.6	25.9	58.7
trans-Broparestrol	10^{-2}	35.2	38.8	35.3	40.4	47.4	47.4	50.1
Broparestrol (60:40)	10^{-3}	36.5	35	38.2	39	43.6	53.5	78.2
Broparestrol (60:40)	10^{-2}	59.6	44.7	46.3	48	45.4	48.5	52.5
cis-Broparestrol	10^{-3}	32	41.9	47.54	58.9	87.8	103.7	108.4
cis-Broparestrol	10^{-2}	60	67.5	70.9	75.25	69.7	73.9	69.8

First of all, it is apparent that all three products are partial agonists and are intermediates between a pure agonist such as Ethinyl oestradiol (high intrinsic activity) and the competitive antagonists (as yet undiscovered antioestrogens).

It is also apparent, however, that the dualist activities of the different products are highly different.

For purposes of clarity, in the case of each compound, Applicant integrated

the areas limited by the dosage effect curve of Ethinyl oestradiol alone and combined. This give an area corresponding to the synergy (1) and an area corresponding to the antagonism (2), as illustrated below.



The percentage and the ratio of said areas permitted quantification of the dualism.

The results of said calculations are reported in Table IV and in the diagram of Fig. 5. This diagram illustrates respectively, for each product: in the left column, the ratio antagonism area/synergy area; and, in the right column, the ratio synergy area/antagonism area.

It is clearly apparent that the *trans*-Broparestrol isomer exhibits a predominant antagonistic effect, whereas the *cis*-Broparestrol isomer exhibits a predominant agonistic effect.

TABLE IV

Product	Dosage g/kg	Synergy area	Antagonism area	Synergy/antagonism	Antagonism/synergy
Trans Broparestrol	10^{-3}	29	106		
	10^{-2}	48	111		
Mean		[38.5] 26.2%	[108.5] 73.8%	0.354	2.81
Broparestrol	10^{-3}	40	63		
	10^{-2}	89	81		
Mean		[64.5] 47.2%	[72] 52.8%	0.895	1.11
Cis Broparestrol	10^{-3}	77	0		
	10^{-2}	109	36		
		[93] 84%	[18] 16%	5.16	0.19

This difference in the dualist action may be evaluated in the following manner.

TABLE V

PRODUCT	DUALISM		LIMIT
	Agonism	Antagonism	
Ethinyl oestradiol	100%	0%	Pure agonist
cis-Broparestrol	84%	18%	Agonistic tendency
Broparestrol	47.2%	52.8%	Partial agonist-antagonist
trans-Broparestrol	26.2%	73.8%	Antagonistic tendency

Thus, the different products modulate the response curve to the oestrogens, but at different levels. Thus, the *trans*-Broparestrol isomer provides a regulation of the effects of oestrogens at relatively low levels, which permits, by substantial cutting down at the top, to prevent the detrimental effects of high oestrogen dosages, and, by slight cutting down at the bottom to retain the indispensable minimum physiological effects. Thus, the *trans*-isomer constitutes a much better regulator of the effects of oestrogens than the *cis*-isomer which induces modulation only at a high level.

II—Prevention of spontaneous mammary tumors in mice $C_3H/_{He}$ submitted to forced reproduction by treatment with *trans*-Broparestrol-Antifertilizing effect in the same animals

a) Preamble

Mammary tumors may develop spontaneously in mice $C_3H/_{He}$ carrying the Bittner viral factor. Accelerated reproduction promotes the formation of such tumors and shortens the period of time preceding their appearance. While other types of experimental mammary tumors induced by cancerogenic materials are hormone-dependent—and whose formation and evolution are relatively readily controlled, the spontaneous tumors in mice $C_3H/_{He}$ are more difficultly controlled. Similarly, the development of such tumors appears to be essentially dependent on an increased secretion of prolactine by the pituitary gland.

b) Material and method

The experiment was conducted in female mice $C_3H/_{He}$ (1n—1e). Only mice bred by Applicant and closely attended to for a number of years were used. Due to suitable caretaking conditions, both where the mothers and the new-born are concerned, the animals may live under good physical conditions for more than two years. The spontaneous death rate is infinitesimal; this authorizes the undertaking of experiments of long duration.

Female mice $C_3H/_{He}$ (1n—1e) were isolated from litters born at 48 hour intervals. At the age of four weeks, animals weighing between 19 and 20 g are selected. Thirty-five females are thus selected; they are each given a number and they are distributed into two groups:

—Group 1: 20 animals, submitted to treatment with *trans*-Broparestrol. 50 mg of product per kg of body weight, diluted with pharmaceutical grade olive oil, are injected sub-cutaneously once a week for 2 months. On completion of the treatment, the females are placed in cages (4 per cage) in the presence of a male and submitted to reproduction.

—Group 2: Reference group. 15 mice are given only the oily excipient, under the same conditions, during a period of time of two months. At the end of that time, they are placed by fours and threes in cages in the presence of a male and submitted to reproduction.

Accelerated reproduction is conducted in the usual manner: immediately after birth, the young are removed and the females are again submitted to the males.

The animals are weighed once a week. The number of gestations and litters, together with the formation of mammary tumors, the period of time prior to their appearance, are individually recorded for each mouse.

The total duration of the experiment is eighteen months.

c) Results

α) Prevention of mammary tumors

After carrying out the experiment for 1.5 year, the development of mammary tumors is markedly lower in the group treated with *trans*-Broparestrol.

In the reference group, except for a mouse sacrificed at the age of 6 months due to a poor systemic condition and which did not carry any tumor, all other mice exhibit mammary tumors. Out of 20 animals preventively treated with *trans*-Broparestrol, there are noted only three cases of mammary tumors. One of the mice, sacrificed at the age of 18 months due to a poor systemic condition, does not carry any mammary tumor. Autopsy of the other mice, at the end of the experiment, did not disclose any tumourous lesion, either in the mammary tissue areas or in the other organs.

The number and percent mammary tumors of each of the groups are reported in Table VI.

Whereas, in the reference group, the percent tumors is 93% (frequent

percentage for this line of mice), treatment with *trans*-Broparestrol reduced the percentage to 15%.

Thus, in the group treated with *trans*-Broparestrol, the development of tumors is markedly lower than that noted in the reference group.

TABLE VI

Inhibition with *trans*-Broparestrol of the development of spontaneous mammary tumors in mice $C_3H/_{He}$

Number of tumors, percent tumors, and time to the appearance of tumors in the reference and treated groups.

Age of the animals (months)	Time of latency (days from the beginning of the treatment)	Animals with mammary tumors			
		Treated group		Reference group	
			%		%
5	103	0	0	0	0
5	110	0	0	1	6.6
6	138	0	0	1	13.3
6	145	0	0	1	20
6	152	0	0	1	26.6
7	166	0	0	2	40
8	194	0	0	1	46.6
8	202	0	0	2	60
9	215	0	0	1	66.6
9	230	0	0	2	80
12	307	1	5	1	86.6
16	432	1	10	0	86.6
18	516	1	15	1	93.3
19 (sacrifice)	547	0		–	
Total		3/20, i.e., 15%		14/15, i.e. 93%	

It should be noted that where the period of time prior to the appearance of the tumors is concerned, there is a marked difference between the two groups. In the reference group, most tumors appear in the animals at the age of 6—9 months. In the group treated with *trans*-Broparestrol, this period of time is extended; the first tumor appears belatedly at the age of 12 months, and the other two at the 16th and 18th month of age.

β) Action of *trans*-Broparestrol on reproduction

After two months of treatment, *trans*-Broparestrol reduces markedly the reproduction in mice.

Among the 20 animals of the treated group, two females only gave birth a

single time, four months after the end of the treatment. It should be noted that one of these two females (mouse n° 9) developed a mammary tumor, 4 months thereafter. The other mouse did not exhibit any tumorous lesion.

During the experiment, the males were changed three times in each of the treated cages. As a comparison, reproduction was normal in the reference group; each female gave birth several times. The number of litters per female varies between three and eleven litters, depending on the more or less early appearance of tumors in said mother-mice.

This contraceptive effect is durable; it extended to the end of the experiment, i.e., 16 months after interruption of the treatment.

d) Conclusion

Early administration of *trans*-Broparestrol (50 mg/kg/s.c./once weekly) from the 1st to the 3rd month of age, in mice $C_3H/_{He}$ submitted to forced reproduction, decreases considerably the development of tumors. Similarly, the time before the appearance of the first tumors is significantly extended in the mice treated with *trans*-Broparestrol.

On the other hand, a durable inhibition of reproduction was noted in the animals treated with *trans*-Broparestrol.

III — Action of *trans*-Broparestrol on fertility

a) Material and Method

The test was conducted in adult Sprague Dawley female rats weighing about 200±10 g distributed into groups of 8 animals each.

Trans-Broparestrol is administered orally for 35 days. The females (groups of 4 females each) are placed in the presence of 2 males from the 6th day of treatment.

The females are isolated and the treatment is interrupted as soon as the females are thought to be fecundate.

The criterion of appreciation is a supranormal weight increase of the fecundate females. The weight increase of reference animals is on the average of 14 g over 12 days, and the fecundate females are isolated after about 12 days when their increase in weight is in excess of 35 g.

trans-Broparestrol was administered at dosages of 10^{-4}, 2.5×10^{-4} and 10^{-3} g/kg.

b) Results

The results obtained are given in Table VII.

The results are expressed as percent anti-fertilizing action. *trans*-Broparestrol has a total anti-fertilizing action at a dosage of 10^{-3} g/kg.

TABLE VII

Dosages	Percent anti-fertilizing activity
10^{-4}	0
2.5×10^{-4}	25
10^{-3}	100

IV — Toxicological investigation of *trans*-Broparestrol

a) Acute toxicity

Acute toxicity was investigated in male and female rats and in male and female mice after administration of *trans*-Broparestrol by two different routes: orally and sub-cutaneously.

Whatever the route of administration, *trans*-Broparestrol is non-toxic.

TABLE VIII

Species	Sex	Route	Maximum dosage administrable	Mortality
Rat	male	oral	4000 mg/kg	Nil
	female	oral	4000 mg/kg	Nil
	male	sub-cutaneous	2000 mg/kg	Nil
	female	sub-cutaneous	2000 mg/kg	Nil
Mouse	male	oral	4000 mg/kg	Nil
	female	oral	4000 mg/kg	Nil
	male	sub-cutaneous	2000 mg/kg	Nil
	female	sub-cutaneous	2000 mg/kg	Nil

No symptom of intoxication is noted on administration of the compound. Behaviour remains normal; no fatal issue was noted after 14 days observation. Autopsy does not disclose any macroscopic lesion of the principal organs; however, a decrease of the weight of the uteri is observed in the females.

b) Long-term toxicity

Long-term toxicity was investigated in male and female rats which were orally administered *trans*-Broparestrol during a period of time of three months at dosages of 1—5—10 and 20 mg/kg/day, respectively. Behavior of the animals remained normal throughout the treatment; no death occurred.

Hematological examination does not disclose any change in the counts and in the hemoglobin content.

As a whole, the modifications of the various biological constants are within the limits of the normal physiological variations in the controls.

Histological examination of the main organs is normal. In male rats, *trans*-Broparestrol has no histologically visible effect on the different viscera of male rats and also no perceivable oestrogenic effect at the level of the endocrine glands. In female rats, the histological structure of all organs is normal, except for the ovaries in which an endocrinic effect is noted at very high dosages.

Examples of administrable formulations containing, as active ingredient, substantially pure *trans*-Broparestrol (i.e., substantially free from *cis*-Broparestrol) are given hereinunder.

1. Tablet containing 10 mg *trans*-Broparestrol

trans-Broparestrol	0.010 g
Lactose	0.130 g
Rice starch	0.045 g
Pregelatinized corn starch	0.006 g
Sodium carboxymethylcellulose	0.002 g
Talc	0.004 g
Magnesium stearate	0.003 g

2. Capsule containing 50 mg *trans*-Broparestrol

trans-Broparestrol	0.050 g
Lactose	0.243 g
Talc	0.005 g
Magnesium stearate	0.002 g

3. Injectable solution containing 5% *trans*-Broparestrol

trans-Broparestrol	0.005 g
Benzyl benzoate	0.001 g
Neutralized olive oil, sufficient to make 1 ml	

Combinations of *trans*-Broparestrol with oral contraceptives themselves consisting of an oestrogen-progestational drug combination, may be formulated as pills, capsules or tablets containing 0.1—5 mg of a progestational agent such as Norgestrel, Norethisterone acetate, Quingestanol acetate or Lynoestrenol, 0.01—0.5 mg of an oestrogen such as Ethinyl oestradiol or Mestranol, and 30—300 mg *trans*-Broparestrol (preferably 50—80 mg).
Examples of such combinations are given below.

1. Ordinary tablet

Mestranol	0.075 mg
Lynoestrenol	2.5 mg
trans-Broparestrol	60 mg
Excipient, sufficient to make one 150 mg tablet (lactose, rice starch, glycerine, talc, magnesium stearate)	

2. Coated tablet

Ethinyl oestradiol	0.05 mg
Norgestrel	0.5 mg
trans-Broparestrol	40 mg
Excipient, sufficient to make one 150 mg coated tablet (lactose, corn starch, gelatin, white wax, carnauba wax, magnesium stearate, methyl paraben, propyl paraben, talc, polyvinyl-pyrrolidone, tricalcium phosphate)	

3. Capsule

trans-Broparestrol	150 mg
Mestranol	0.075 mg
Lynoestrenol	2.5 mg
Lactose	143 mg
Talc	5 mg
Magnesium stearate	2 mg

WHAT WE CLAIM IS:—

1. Therapeutic composition comprising *trans*-Broparestrol isomer as active ingredient and being substantially free of the *cis*-isomer, together with a pharmaceutically acceptable carrier.

2. Composition as claimed in claim 1, formulated in a form suitable for oral administration.

3. Composition as claimed in claim 2, in unit dosage form, each unit dose containing 10—300 mg *trans*-Broparestrol isomer.

4. Composition as claimed in claim 1, formulated in a form suitable for subcutaneous administration.

5. Composition as claimed in claim 4, consisting of an injectable solution in a pharmaceutically acceptable solvent.

6. Composition as claimed in claim 5, formulated as ampoules containing each 3—200 mg *trans*-Broparestrol isomer.

7. Composition as claimed in claim 2, wherein there is additionally present an oral contraceptive consisting of an oestrogen-progestational agent combination.

8. Composition as claimed in claim 7, comprising 0.1—5 mg of a progestational agent, 0.01—0.5 mg of an oestrogen, and 30—300 mg *trans*-Broparestrol.

9. Composition as claimed in claim 1, substantially as described in any one of the formulation examples herein.

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3 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

FIG. 1

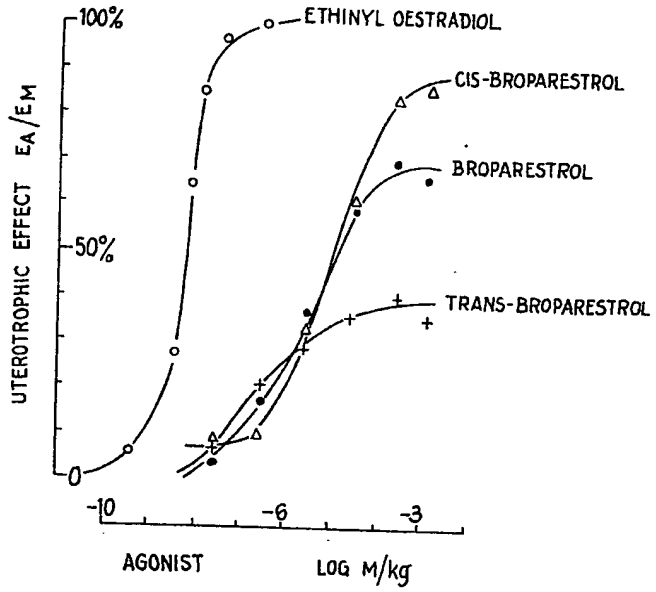


FIG_4

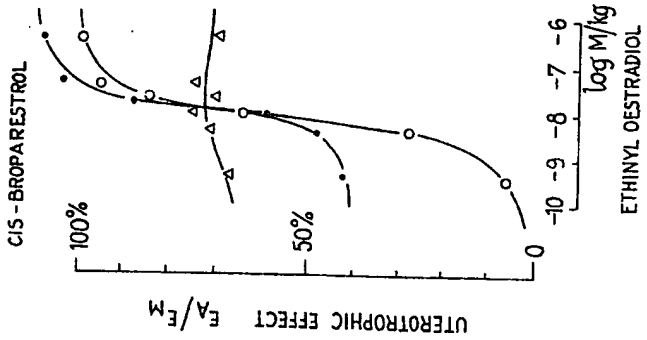


FIG_3

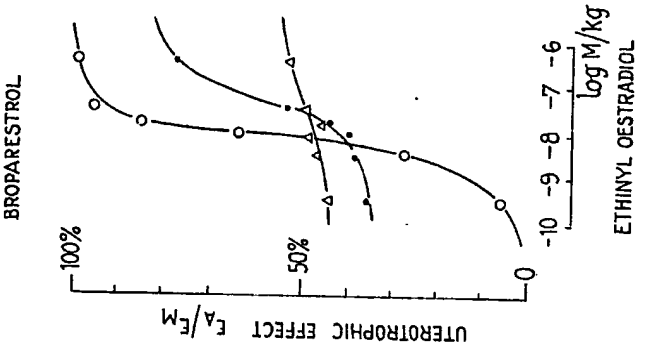


FIG_2

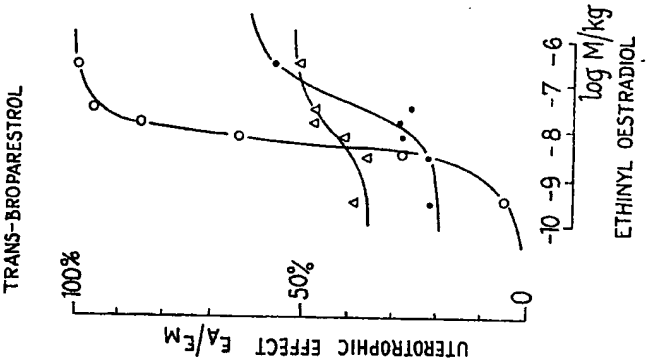
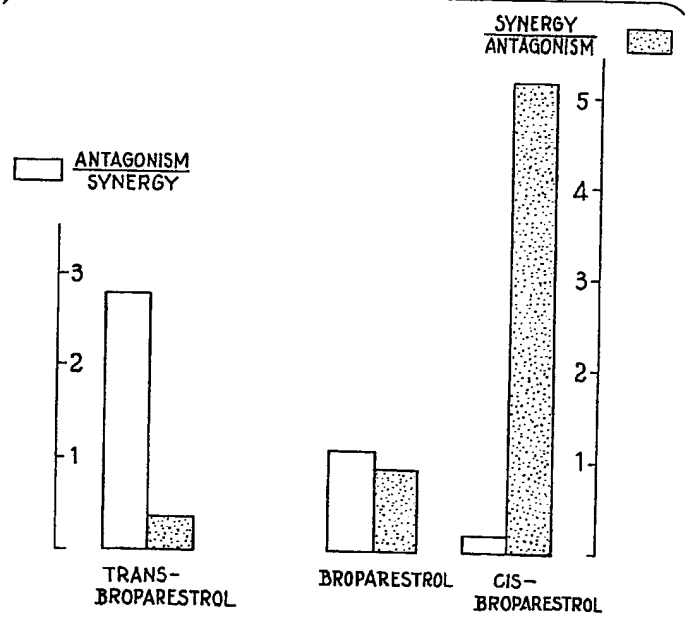


FIG_5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